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High Rates of Smoking Especially in Female Crohn's Disease Patients and Low Use of Supportive Measures to Achieve Smoking Cessation—Data from the Swiss IBD Cohort Study

Luc Biedermann,[a] Nicolas Fournier,[b] Benjamin Misselwitz,[a] Pascal Frei,[c] Jonas Zeitz,[a] Christine N. Manser,[a] Valerie Pittet,[b] Pascal Juillerat,[d] Roland von Känel,[e] Michael Fried,[a] Stephan R. Vavricka,[f] Gerhard Rogler;[a] for the Swiss Inflammatory Bowel Disease Cohort Study Group

[a]Division of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland [b]Institute of Social and Preventive Medicine, University of Lausanne, Lausanne, Switzerland [c]Division of Gastroenterology & Hepatology, Seespital Horgen, Horgen, Switzerland [d]Division of Gastroenterology & Hepatology, Inselspital Bern, Bern, Switzerland [e]Department of Psychosomatic Medicine, Clinic Barmelweid, Barmelweid, Switzerland [f]Division of Gastroenterology & Hepatology, Triemli Hospital, Zurich, Switzerland

Corresponding author: Dr Luc Biedermann, Division of Gastroenterology and Hepatology, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland. Tel.: +41-44-255-9519; fax: +41-44-255-9497; email: luc.biedermann@usz.ch

Abstract

Background and aims: Smoking is a crucial environmental factor in inflammatory bowel disease [IBD]. However, knowledge on patient characteristics associated with smoking, time trends of smoking rates, gender differences and supportive measures to cease smoking provided by physicians is scarce. We aimed to address these questions in Swiss IBD patients.
Methods: Prospectively obtained data from patients participating in the Swiss IBD Cohort Study was analysed and compared with the general Swiss population [GSP] matched by age, sex and year.
Results: Among a total of 1770 IBD patients analysed [49.1% male], 29% are current smokers. More than twice as many patients with Crohn's disease [CD] are active smokers compared with ulcerative colitis [UC] [UC, 39.6% vs CD 15.3%, $p < 0.001$]. In striking contrast to the GSP, significantly more women than men with CD smoke [42.8% vs 35.8%, $p = 0.025$], with also an overall significantly increased smoking rate compared with the GSP in women but not men. The vast majority of smoking IBD patients [90.5%] claim to never have received any support to achieve smoking cessation, significantly more in UC compared with CD. We identify a significantly negative association of smoking and primary sclerosing cholangitis, indicative of a protective effect. Psychological distress in CD is significantly higher in smokers compared with non-smokers, but does not differ in UC.
Conclusions: Despite well-established detrimental effects, smoking rates in CD are alarmingly high with persistent and stagnating elevations compared with the GSP, especially in female patients. Importantly, there appears to be an unacceptable underuse of supportive measures to achieve smoking cessation.

Keywords: Smoking; gender differences; smoking cessation

1. Introduction

Smoking has a crucial impact on the clinical course and response to treatment in inflammatory bowel disease [IBD].[1,2,3,4,5,6] It can be considered the most extensively investigated and replicated environmental factor in IBD.[7,8]

Tobacco smoking has a clearly detrimental impact on the course of CD and increases the likelihood of stricturing and fistulising phenotype.[9] In contrast, in UC smoking has a protective effect, with a substantially elevated risk of developing UC in former smokers compared with patients who never smoked [1,6,10,11,12,13] and a milder course of the disease in former smokers who resume smoking.[3,14] Moreover, whereas active smoking is a risk factor for developing early-onset CD, in UC the same holds true for previous smokers.[15,16] However, the reasons underlying the divergent impact of smoking on CD vs UC largely remain obscure.[17]

Smoking also influences the response to medical and surgical treatment. Among the factors associated with failure of anti-tumour necrosis factor [TNF] treatment for instance, ongoing smoking is important in CD,[18,19] and interestingly also in other systemic immune diseases such as rheumatoid arthritis.[20] Moreover, in CD smoking is a risk factor of primary intestinal resection[21] and recurrence of stricture formation after dilation,[22] and has been identified to be the strongest risk factor for postoperative recurrence, roughly doubling the risk.[23,24,25] On the other hand, smoking cessation appears to have a beneficial impact on the further course of disease in CD.[1,12]

The mechanisms through which smoking affects the [divergent] course of disease in IBD are complex and hitherto only incompletely understood. Presumably a multitude of factors play a role, such as direct effects of various components of tobacco smoke [including nicotine, free radicals, and carbon monoxide] on several effector targets, above all the mucus layer, the immune system function [cytokines, macrophage function], the microvasculature, and potentially also epigenetics.[8,17] Moreover, evidence on a direct effect of smoking status on intestinal microbial composition is increasing.[26,27,28] Unfortunately and in contrast to what has previously been assumed, therapeutic effects of nicotine replacement in UC are limited, with a risk of side effects.[29]

Current European CD guidelines advocate encouraging smoking cessation,[30] whereas no such statement can be found in the respective UC guidelines.[31,32] In UC, given the well-established beneficial effects of continuous smoking[13] or low-dose smoking resumption in ex-smokers,[33] many physicians might hesitate to advocate smoking cessation in UC patients. Yet in CD patients, there are only scarce data on the magnitude of support provided by treating physicians to cease smoking. Furthermore, knowledge on time trends of smoking rates in IBD patients compared with the general population is very limited.

Using data of the Swiss IBD Cohort Study [SIBDCS], a large, prospective, nationwide cohort study in Switzerland, we aimed to analyse patient characteristics associated with smoking including potential differences in terms of gender and education, psychological distress, and quality of life [QoL], and timetrends of smoking rates, as well as support received to cease smoking.

2. Materials and Methods

2.1. Swiss IBD Cohort Study

The SIBDCS is a nationwide disease-oriented prospective cohort study, having included patients from all over Switzerland since 2006.[34] The cohort study has been approved by all local ethical committees and receives continuous support from the Swiss National Science Foundation. All patients are followed up once a year and additionally in case of unscheduled events, such as a flare or hospitalisation. An annual questionnaire is sent to the patients covering the clinical disease course and various additional aspects including psychosocial distress and QoL. All patients provided written informed consent to participate in the study.

2.2. Data extraction, definitions

Details on the methodology of data extraction are described elsewhere.[34] Patients were defined as smokers or non-smokers based on self-declaration from patients' questionnaires. We deliberately decided against using data from the physicians' questionnaires to define smoking status, as it appears plausible that some smoking patients might not disclose their smoking status as appropriately as anonymously. Data regarding support to cease smoking as well as other factors associated to smoking status, such as level of education or country of origin, were also extracted from the patients' questionnaires. Information on disease location and primary sclerosing cholangitis [PSC] was extracted from the physicians' questionnaires. Data on the prevalence of smoking in the GSP was obtained from a recent official monitoring report on the consumption of tobacco in Switzerland from the Bundesamt für Gesundheit der Schweiz [Swiss Federal Office for Public Health].[35] In this continuous survey on tobacco consumption, comprising an integral component of the Addiction Monitoring in Switzerland commissioned by the Swiss Federal Office for Public Health, a random sample of 2750 persons are surveyed every 3 months with general questions on the consumption of alcohol, tobacco, and other substances [core sample; among them 250 persons by mobile phone, the rest by a fixed network telephone interview; yielding a core sample set of 11 000 persons annually], whereas subsequent in-depth questions are posed in two split samples [1:1, Split A with alternating topics, Split B with an unchanged additional core with detailed information on tobacco consumption].

2.3. Psychological and quality of life measures

To assess psychological distress related to symptoms of anxiety and depression, we used the Hospital Anxiety and Depression Scale [HADS], a validated psychometric instrument with a subscale for anxiety [HADS-A] and depression [HADS-D]. Each subscale comprises seven items which are scored on a four-point Likert scale [0 = not at all, 3 = mostly] covering the previous 7 days; total scores for the HADS-A and HADS-D range between 0 and 21, with higher scores indicating greater levels of distress from anxiety and depression, respectively.[36,37] Total scores are clinically interpreted with the following cut-off points: 0–7: no anxiety/depression; 8–10: mild anxiety/depression; 11–14: moderate anxiety/depression; 15–21: severe anxiety/ depression. Although as a self-rating instrument the HADS does not allow for a formal diagnosis of a psychiatric disorder, a score ≥ 8, defining the threshold for clinically relevant symptoms, has been shown to identify a major depressive disorder with a sensitivity of 82% and a specificity of 74%.[38] The HADS has been validated multiple times not only in psychiatric but also somatic patients, as well as in the general population.[39]

The Short Form 36 Health Survey [SF-36] represents a questionnaire with 36 items on eight different dimensions, namely physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, mental health, and general health, designed to survey health status in a medical outcome study.[40] For each of the subscales possible, scores range from 0 to 100 with a higher score representing a better health status.[40,41] The SF-36 has been used in numerous clinical trials, including a variety of studies on gastrointestinal diseases.[42] Due to its high reliability and validity, the SF-36

is considered to represent a valuable tool to measure health-related QoL.[42]

2.4. Statistical analysis

For statistical analysis we used SPSS [version 21; IBM, Armonk, NY, USA], Prism [version 6, GraphPad Software, La Jolla, CA, USA], and STATA [version 13.1, StataCorp, College Station, TX, USA] with level of significance set at a p-value ≤ 0.05. For a comparison of smoking rates within the cohort between males and females and CD vs UC patients, chi-square-testing was used. Chi-square was also applied to test for differences in having received support to cease smoking, an association between smoking and PSC, and an association of smoking status and disease location, as well as for the exploration of other factors associated with smoking. To compare smoking rates within the cohort to the GSP, CochranArmitage testing was used. Regarding the comparison of HADS and SF-36 scores between smokers and non-smokers, a Wilcoxon MannWhitney rank-sum test was applied.

3. Results

3.1. Smoking rates overall and per type of IBD and sex

We analysed data from a total of 1770 IBD patients [49.1% male, 56.7% with CD], ie all patients included in the cohort at the time of data extraction October 2012, where smoking status was available [80.2% of all patients included in the cohort at that point in time]. Overall, 29% of all IBD patients in the SIBDCS are current smokers, but smoking rates differed substantially between type of IBD and sex [Figure 1]. More than twice as many patients with CD are active smokers compared with UC [39.6% vs 15.3%, $p < 0.001$]. In striking contrast to the GSP, where smoking rates in men are consistently higher compared with women throughout all age groups, significantly more women than men with CD smoke [42.8% vs 35.8%, $p = 0.025$]. In contrast, in UC patients there is no significant difference in smoking rates between women and men [13.2% vs 17%].

3.2. Smoking rates according to age groups and in comparison with the GSP

Comparing IBD patients overall with the GSP, smoking rates are roughly identical, with 29% in SIBDCS patients and 27% in the GSP [age 14–65, year 2010]. In terms of specific age groups, slight differences in smoking rates in the SIBDCS between 15 and 54 years of age and lower rates in the age group 55–65 appear to parallel those of the GSP. Significantly more women with IBD in the age groups 35–44 and 45–54 years smoke compared with their counterparts in the GSP [whereas there is a non-significant trend of lower smoking rates in male IBD patients Figure 2A]. In CD, women smoke significantly more often than in the GSP throughout all age groups, whereas smoking rates in men are similar to the GSP [Figure 2B]. Indeed, the highest smoking rate observed at all [51.7%] is found in women with CD aged 45–54 years, which is virtually twice as high as in the age- and sex-matched GSP [26.6%, $p < 0.001$]. In contrast, the smoking rates in UC are lower than in the GSP, with significant differences throughout most age groups [Figure 2C].

Since receiving an IBD diagnosis [especially the diagnosis of CD] early in life might modify subsequent smoking behaviour, we tested smoking rates according to age at IBD diagnosis. Age of diagnosis is not significantly associated with smoking rates in either CD or UC [in female CD patients, there is a non-significant lower smoking rate among those having received their diagnosis before the age of 20 compared with their counterparts who received their diagnosis thereafter, with 38.8% vs 43.8%].

3.3. Time trends of smoking rates in recent years

In the GSP, smoking rates have decreased from 2001 to 2012. We observe decreasing smoking rates on a similar level in Swiss IBD patients [Figure 3A]. However, looking at CD and UC patients separately, persistently higher smoking rates above the GSP can be observed in CD patients in our cohort [Figure 3B]. Of note, there is indication for a potential *de novo* rise in female patients, both in those with UC and those with CD [Figure 3B, C].

3.4. Support to cease smoking

All patients smoking when receiving their IBD diagnosis were asked [at inclusion in the SIBDCS] whether they previously had received any support to achieve smoking cessation. Among all smoking IBD patients, the majority [90.5%] claim to never have received any support to cease smoking. This number is significantly higher in UC compared with CD patients [97.4% vs 88.1%, $p < 0.001$]. We do not observe any differences in claimed support according to sex, age-group, level of education or country of origin. Among the 9.5% of patients having received support, 2.2% of the total received a specialised consultation [structured smoking cessation programme] and 4.3% were counselled by their treating general physician [other form of support: 3%, Figure 4].

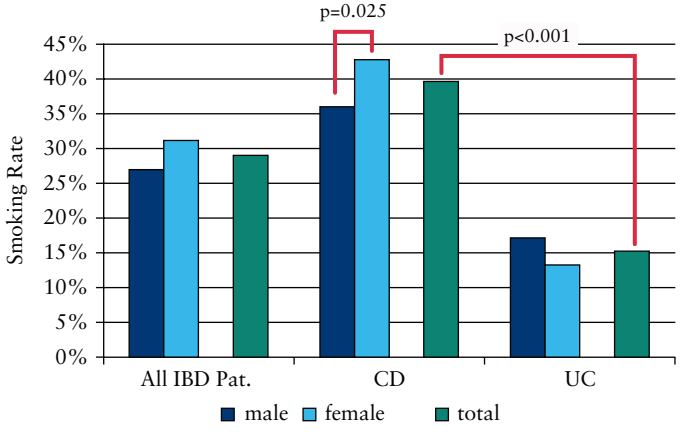

Figure 1. Smoking rates among inflammatory bowel disease [IBD] patients overall and according to type of IBD and sex. Significant differences are highlighted in purple with respective p-values indicated.

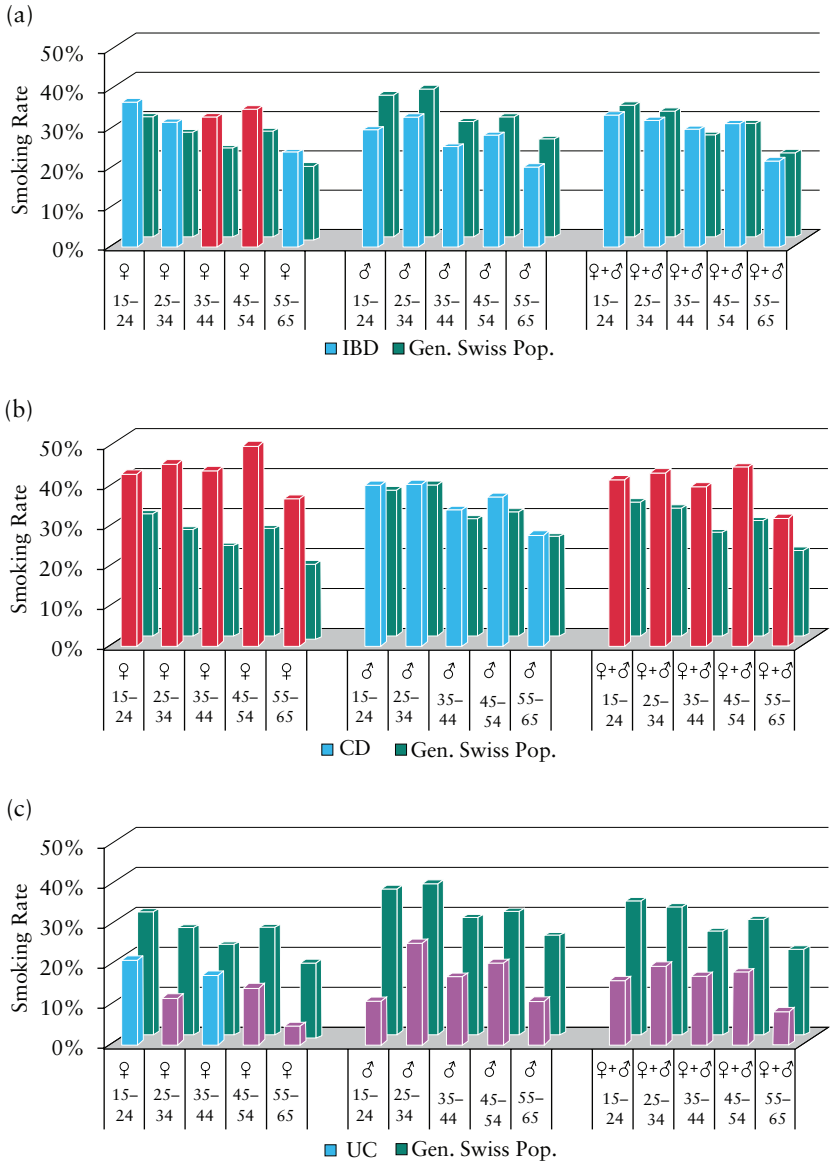

Figure 2. Smoking rates across age groups for: inflammatory bowel disease [IBD] overall [A]; Crohn's disease [CD] [B]; and ulcerative colitis [UC] [C]. Significance is indicated by colour of the bars with higher rates in comparison with the general Swiss population [GSP] depicted in red [A, B] and lower rates in green [C].

3.5. Smoking and PSC

In total, there are 26 patients [1.5% of all SIBDCS patients analysed] with a concomitant diagnosis of PSC [0.4% of CD and 3% of UC patients, respectively], in line with the lower end of the reported prevalence in the literature.[43] Due to the relatively small sample size of IBD-PSC cases, any conclusions have to be drawn with caution. Of note, however, is that within our cohort only one single PSC patient [female, concomitant CD] was a smoker. All other PSC cases were non-smokers, revealing a significant negative association between smoking and the occurrence of PSC in IBD [p = 0.002]. This negative association was significant among patients with UC [p = 0.04] but not in CD. However, with only 4 cases of PSC with CD, our study is underpowered for testing in CD. According to our data, the negative association of smoking and PSC might be of special relevance in male patients [Figure 5].

3.6. Smoking and disease location

Whereas smoking rates are significantly lower in UC compared with CD patients, there is a non-significant trend towards an increased fraction of extensive disease with pancolitis in smoking compared with non-smoking UC patients [47% vs 38.3%; p = 0.077, non-significant]. Among CD patients, a significantly lower abundance of isolated colonic disease [L2 according to the Montreal Classification] can be observed in smokers vs non-smokers [24% vs 33.7%, p = 0.001 Figure 6].

3.7. Patient characteristics associated with smoking

Next, we investigated specific patient characteristics for a potential association with smoking status. An overview of these correlates of smoking is provided in Table 1. Having children is significantly associated with a lower probability of active smoking in female but not in male IBD patients. Of note, IBD patients born in Switzerland are significantly more often active smokers compared with patients born in foreign countries. A higher formation level [higher job training or university] is associated with lower smoking rates in IBD overall and in CD but not in UC. Moreover, receiving an invalidity pension is the strongest risk factor for smoking of all patient characteristics tested. As might be expected, regular physical activity [defined as doing sports at least once

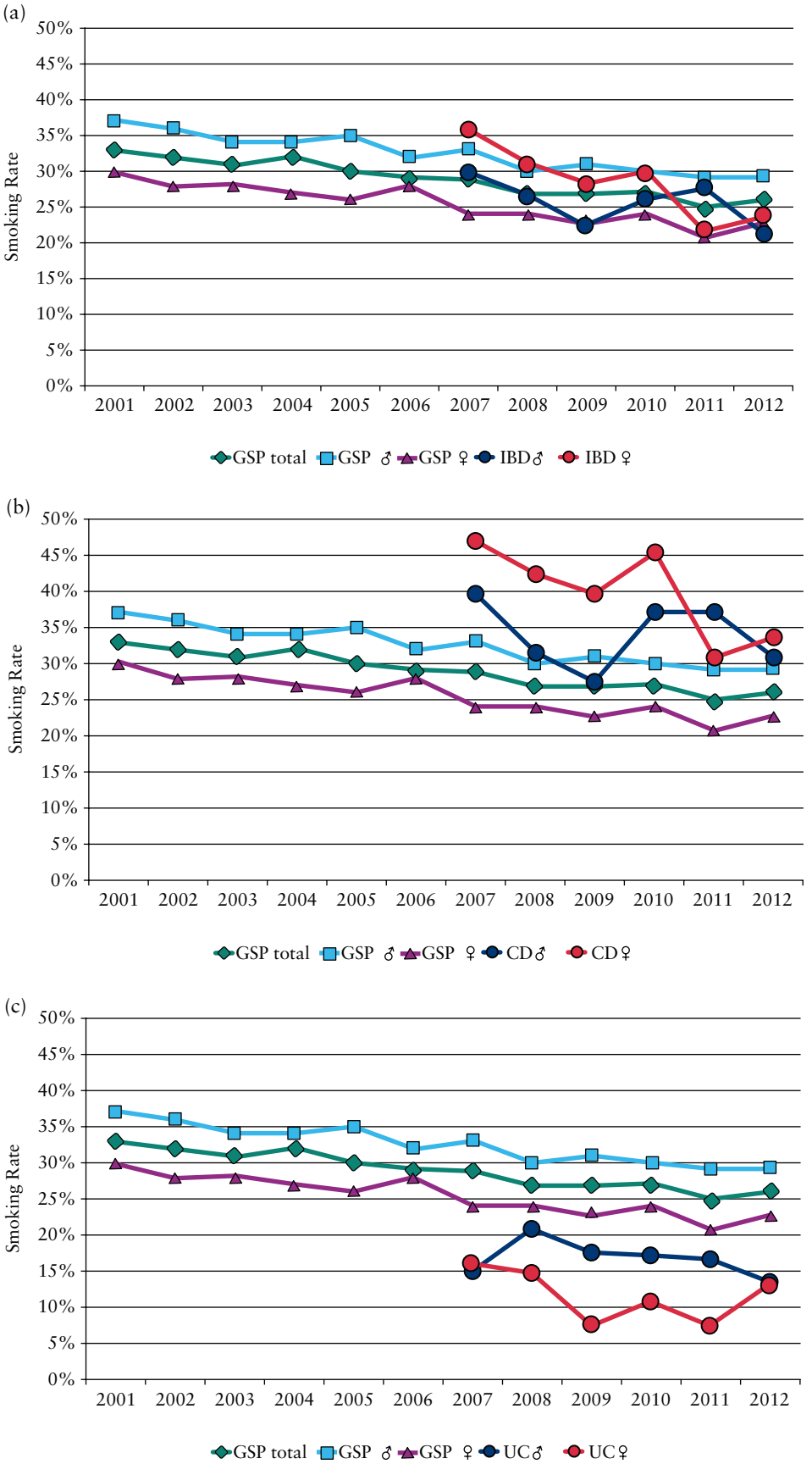

Figure 3. Smoking rates [y-axis] of male [blue] and female [red] inflammatory bowel disease [IBD] patients are depicted at the year of inclusion in the cohort in comparison with the general Swiss population [GSP] for: all IBD [A]; Crohn's disease [CD] [B]; and ulcerative colitis [UC] [C] patients.

a week] appears to be associated with lower smoking rates. Frequent consumption of alcohol appears to be associated with smoking. While we do not observe a significant increase of moderate consumption [ie between once per week and less than daily], significantly more smoking vs non-smoking patients with UC [13.1% vs 6.9%] and smoking vs non-smoking men with IBD overall [16.7% vs 10.1%] claim to consume alcohol at least once per day, equalling a relative risk [RR] of being a smoker of 1.91 [$p = 0.02$] and 1.65 [$p = 0.01$], respectively.

3.8. Features of complicated course of disease associated with smoking

We do not observe a significant increase in the risk of the composite 'any complications', corresponding to a relative risk of 1.03 (confidence interval [CI] 0.92–1.15), 1.01 [CI 0.84–1.14], and 0.82 [CI 0.63–1.08] for smoking vs non-smoking IBD overall, CD, and UC, respectively. The same holds true for its individual complications, such as anaemia, perforation and peritonitis, colorectal dysplasia or cancer, gallstones, nephrolithiasis, massive haemorrhage, deep vein thrombosis, or pulmonary embolism. However, the relative risk of current or past fistula formation is increased in smoking vsnon-smoking IBD patients [RR 1.64; CI 1.35–1.98, $p < 0.001$], and so is the relative risk of current or past abscess [RR 1.58; CI 1.23–2.02, $p < 0.001$]. Likewise, there is an increased risk of current or past stenosis [RR 1.74; CI 1.46–2.09, $p < 0.001$], hospitalisation [RR 1.19; CI 1.02–1.39, $p = 0.034$], as well as surgery [RR 1.36; CI 1.19–1.54, $p < 0.001$] in smoking vs non-smoking IBD patients. With regard to medical treatment, current anti-TNF administration is significantly more prevalent in smoking IBD patients, with a relative risk of 1.57 [CI 1.30–1.90, p <0.001], which seems to be even more pronounced in women [RR 1.74; CI 1.36–2.23, $p < 0.001$] compared with men [RR 1.34; CI 1–2.10, $p = 0.056$, not significant]. Concerning current use of steroids, we do not observe significant differences between smoking and non-smoking IBD patients.

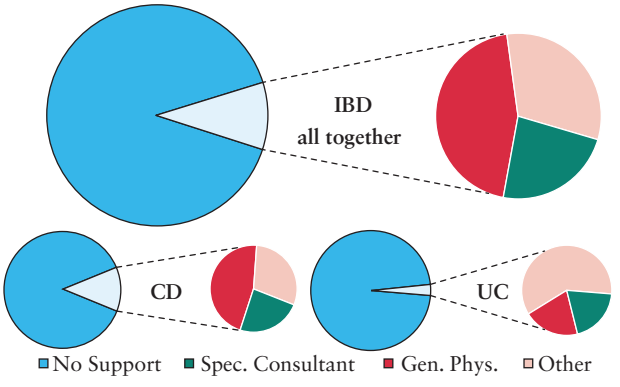

Figure 4. Pie charts depicting support received for smoking cessation. The pie chart on the top represents all inflammatory bowel disease [IBD] patients, whereas the lower charts indicate support provided for Crohn's disease [CD] and ulcerative colitis [UC] patients separately. Spec, specialised; Gen, general.

3.9. Psychological aspects associated with smoking and quality of life

Symptoms of anxiety and depression are both significantly associated with active smoking in both female and male CD patients [$p = 0.001$ and $p = 0.004$ for HADS-A and $p = 0.001$ and $p < 0.001$ for HADS-D sub-score in males and women, respectively]. In contrast, no differences in the levels of anxiety and depressive symptoms are observed in smoking vs non-smoking UC patients in either of the sexes [Figure 7 A,B].

In terms of the SF36 sub-scores, there are significantly higher values [ie better mood and less disability] in non-smoking male and female CD patients relative to their smoking CD counterparts [$p = 0.005$ and $p < 0.001$ for mood; $p = 0.023$ and $p = 0.023$ for disability in male and female patients, respectively Table 2]. Again, no such differences are observed in UC.

4. Discussion

Smoking can be considered the environmental factor in IBD that has most extensively been investigated. However, various smoking-related issues are still open to question. In this study, we describe differences in smoking rates according to the type of IBD, gender, age, and time, and identify differences in the clinical course of smoking vs non-smoking IBD patients. In addition, we address the provision of support to cease smoking by physicians for their IBD patients. Our

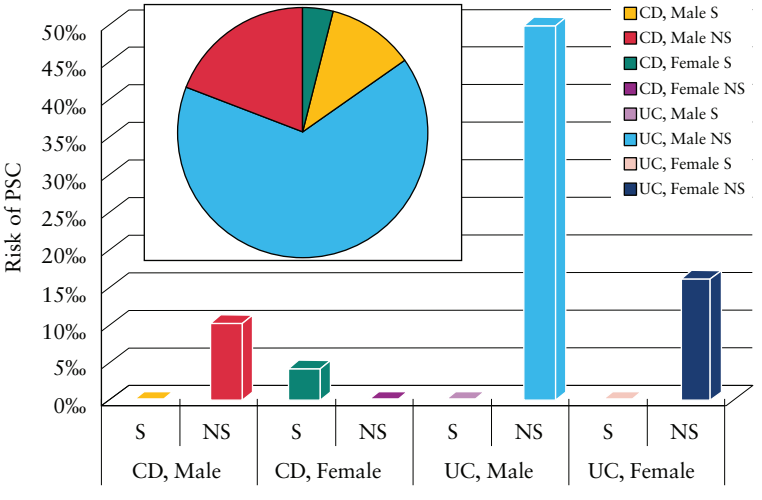

Figure 5. The risk of a concomitant diagnosis of primay sclerosing cholangitis [PSC] in inflammatory bowel disease [IBD] patients is shown in per mille (‰, i.e. parts per thousand) according to sex, smoking status [S, smoking; NS, non-smoking] and type of IBD. Of note, in the SIBDCS the calculated risk is extremely low [approaching zero] in smoking IBD patients with only one single PSC case among smoking patients (a female Crohn's disease [CD] patient). In the inlet on the upper left, the fraction of all PSC cases according to type of IBD, smoking, status and sex is shown in the pie chart.

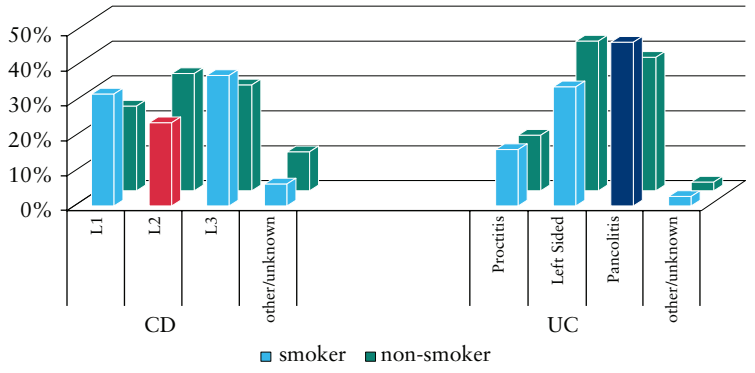

Figure 6. Distribution of disease location for Crohn's disease [CD] [left side] and ulcerative colitis [UC] [right side] according to smoking state in percent [y-axis]. A significantly lower percentage of isolated colonic disease [L2] can be observed in smokers [highlighted in red]. In UC there is a non-significant trend for an increased abundance of pancolitis in smoking patients [highlighted in blue].

data indicate an alarmingly high prevalence of smoking, especially in women with CD [42.8%]. In this subgroup of patients, we identified the highest smoking rates of all, by far exceeding the smoking rates in the GSP throughout all age groups. Thus, our data identify women with CD as an important subgroup of IBD patients, where efficient and goal-directed counselling and support of medical professionals involved in the care of IBD patients is of particular necessity in achieving smoking cessation.

The significant higher rates of active smokers with CD compared with UC appears to be in line with the situation in Europe overall, where this phenomenon can be observed in western and eastern parts of the continent equally.[15] However, to the best of our knowledge, this is the first study reporting on this unexpected and significant gender difference in CD. A former French study focusing on 'ever smokers' and the effect of smoking on the course of colitis in both UC and CD revealed comparable smoking rates in CD between genders, with a slight male preponderance.[44]

Even though our analysis of associations cannot deconstruct the chain of cause and effect, we identified an increased psychosocial burden in smoking CD patients, as indicated by significantly higher levels of distress from anxiety and depressive symptoms and lower QoL. Anxiety and depression might on the one hand explain smoking behaviour but on the other hand also point to therapeutic options. Thus, our findings call for a need of increased awareness among physicians involved in the care of IBD patients, including for instance a low threshold for depression screening and provision of psychological support, especially in female CD patients. Clearly, such screenings need to result in better patient care to be cost effective, as has been discussed elsewhere.[45] Other high-risk groups of patients with specific needs for efficient counselling identified by our study are patients with a lower education level and those receiving an invalidity pension. Presumably, this may not extensively differ from the situation in the GSP. However, in view of the well-established devastating effect of smoking on the disease course in CD, probably potentiating the deleterious psychosocial effect of CD in itself on the one hand and impaired fitness for employment on the other, specific efforts from treating gastroenterologists appear mandatory in the latter subgroup of patients in particular. Moreover, the significant association of smoking and frequent [ie at least once daily, thus presumably deleterious] alcohol use should be recognised, specifically enquired about and considered as a potential adverse co-factor when provision of support to cease smoking is evaluated by the treating physician.

Counselling towards smoking cessation is an effective and cost-effective medical intervention, and even a brief health education combined with advice to stop smoking successfully increase the fraction of quitters, remaining abstinent for 1 year or beyond.[46] Importantly, the vast majority of our patients did not recall any intervention by physicians regarding smoking cessation. Nevertheless, it should be borne in mind that individual patients may judge differently as to what type of action by the treating physician should be defined as support. For instance, whereas one patient may acknowledge a one-time encouraging statement from his treating physician as 'support', another patient may only declare having received support if he or she received a structured form of counselling on the different methods available for smoking cessation or an offer for referral to a specialist consultation. Furthermore, declaration of lacking support indeed might serve as a strategy to avoid self-awareness of one's own insufficient motivation, discipline, and purposefulness, by transferring responsibility away from oneself to the treating physician, at least in some patients. Even though not all interventions might be remembered by patients and there may be heterogeneity in acknowledging any previous attempt of the physician to promote smoking cessation by patients [either involuntary or voluntary], our data point to missed opportunities for our patients. However, the ideal approach for counselling IBD patients remains unknown and future intervention studies are needed to devise efficient strategies. Intuitively, an early diagnosis of IBD might have an impact on the subsequent uptake of smoking habits. However, in our analysis a diagnosis of Crohn's disease as a teenager had no detectable protective effect on subsequent smoking behaviour. The absence of any significant protection may be considered indicative of a lack of effective counselling of young patients regarding the potentially devastating impact of smoking status on the course of their disease, thus reinforcing our above-mentioned conclusion.

In this regard, it is noteworthy that the genetic basis of CD and UC seem similar and the majority of single nucleotide polymorphisms [SNPs] associated with IBD increase the risk of both CD and UC.[47] Accordingly, the genetic background would mostly shape the general IBD risk and environmental factors would influence the type of IBD. Our data, in line with previous studies suggesting that smokers tend to develop deep penetrating inflammation associated with CD and fistulas but are protected from the superficial inflammation of UC, reinforce the relevance of smoking as representing one of the strongest environmental factors having an impact on the specification of IBD in patients at risk. Of note, smoking cessation is the only modification of an environmental risk factor with robust evidence for a beneficial effect on disease course in CD.[29,48]

Regarding disease location, the observed association of smoking state and lower occurrence of isolated colonic disease [L2] in CD is

Table 1. Smoking risk according to patient characteristics.

Factor	Patient group	Relative risk of being a smoker	Significance
Having children	All IBD	0.95	n.s.
	Male IBD	0.98	n.s.
	Female IBD	0.92	0.020
Related person with IBD	All IBD	1.00	n.s.
Country of birth [Switzerland vs other country]	All IBD	1.20	0.05
	All UC	1.22	n.s.
	All CD	1.20	n.s.
Higher job training / university	All IBD	0.85	0.028
	All UC	1.19	n.s.
	All CD	0.80	0.007
Invalidity pension	All IBD	1.83	< 0.001
	All UC	1.57	n.s.
	All CD	1.54	< 0.001
Low physical activity [sport less than once a week]	All IBD	1.43	< 0.001
	All CD	1.42	< 0.001
	All UC	1.08	n.s.
Consumption of alcohol, every day [at least once daily]	All IBD	1.31	n.s.
	IBD, men only	1.65	0.01
	IBD, women only	0.89	n.s.
	All UC	1.91	0.027
	All CD	1.08	n.s.
Consumption of alcohol, rarely [less than once per week] or never	All IBD	0.95	n.s
	IBD, men only	0.81	0.022
	IBD, women only	1.0	n.s.
	All CD	0.99	n.s.
	All UC	0.68	0.001

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; n.s., non significant.

noteworthy. It might be speculated that smoking exerts its influence via a positive modulation of the mucus layer predominantly in the colon, covering and protecting the mucosa, and/or a direct effect on intestinal microbial composition. Regarding the well-established microbial alterations in both subtypes of IBD, smoking may play a role, as recently suggested in a study comparing mucosa-associated microbial composition between smoking and non-smoking CD patients,[26] and in our previous pilot study of healthy smokers undergoing smoking cessation.[27,28] The impact of smoking state on intestinal microbial composition might differentially affect the ileal and colonic mucosa-associated microbiota and hence vulnerability towards and inadequate immune response against microbial antigens.

Our study, in concordance with the increasing body of evidence from the literature,[49,50,51,52] suggests that smoking is a protective factor for the development of PSC in both UC and CD patients. The negative association of smoking with concomitant PSC appears to strongest in UC [Figure 5]. However, since we did not detect a single case of PSC in smoking UC patients, no hazard ratio regarding PSC in non-smokers vs smokers can be calculated. Similar to the aforementioned investigations on risk of PSC according to smoking status, our study cannot serve as a mechanistic investigation on the underlying mechanism for the apparent benefit of cigarette smoking in IBD-PSC, for which the pathophysiology has not been sufficiently clarified.[51] Of note, this protective effect appears to be independent of the well-known impact of smoking in UC, as the beneficial effect of smoking has likewise been observed in non-IBD PSC.[51] Presumably, systemic effects of cigarette smoke may play a role, such as alterations in cellular[53] and humoral[54] immunity, intestinal[27,28] and potentially also biliary microbial composition, adrenal axis, and/or colonic mucus production.[55,56,57]

There is growing evidence of an increased colorectal cancer [CRC] risk in smokers in the general population,[58] but smoking protects from PSC [see above]. Thus one might speculate that smoking might even have a paradoxical protective effect on colorectal cancer in IBD, as PSC has consistently been shown to increase the overall risk of colorectal cancer in IBD with a roughly 5-fold relative risk.[59] Testing for a negative association of smoking on CRC development in our cohort is limited by the small number of CRC cases. Nevertheless, it appears noteworthy that 8 out of 10 CRC cases occurred in non-smokers and 6 UC patients developing CRC were non-smokers. In any case, the detrimental health effects of smoking are undisputed, and patients with both CD and UC were recently shown to have a significantly increased risk of smoking-associated extraintestinal cancers, with a standardised incidence ratio of 1.3,[60] further underscoring the importance of smoking cessation in IBD patients.

Our study has several limitations. The SIBDCS is not fully population-based in that IBD patients recruited in hospitals are somewhat overrepresented. In addition, our data regarding smoking, psychological health, and socioeconomic status rely entirely on patient reporting and might be subject to some level of involuntary or voluntary recall bias. However, the latter may be even more of concern, if questions regarding smoking are directly posed and recorded by physicians or other healthcare professionals, which is why we decided to only use the patient questionnaires' data on smoking. Obtaining information on such a sensitive topic as consumption of a noxious substance is evidently a cumbersome process and prone to various potential sources of bias. Any information on the number of cigarettes smoked per day as well as duration of smoking could have been of interest for our analyses. Unfortunately, no quantitative information on smoking is recorded

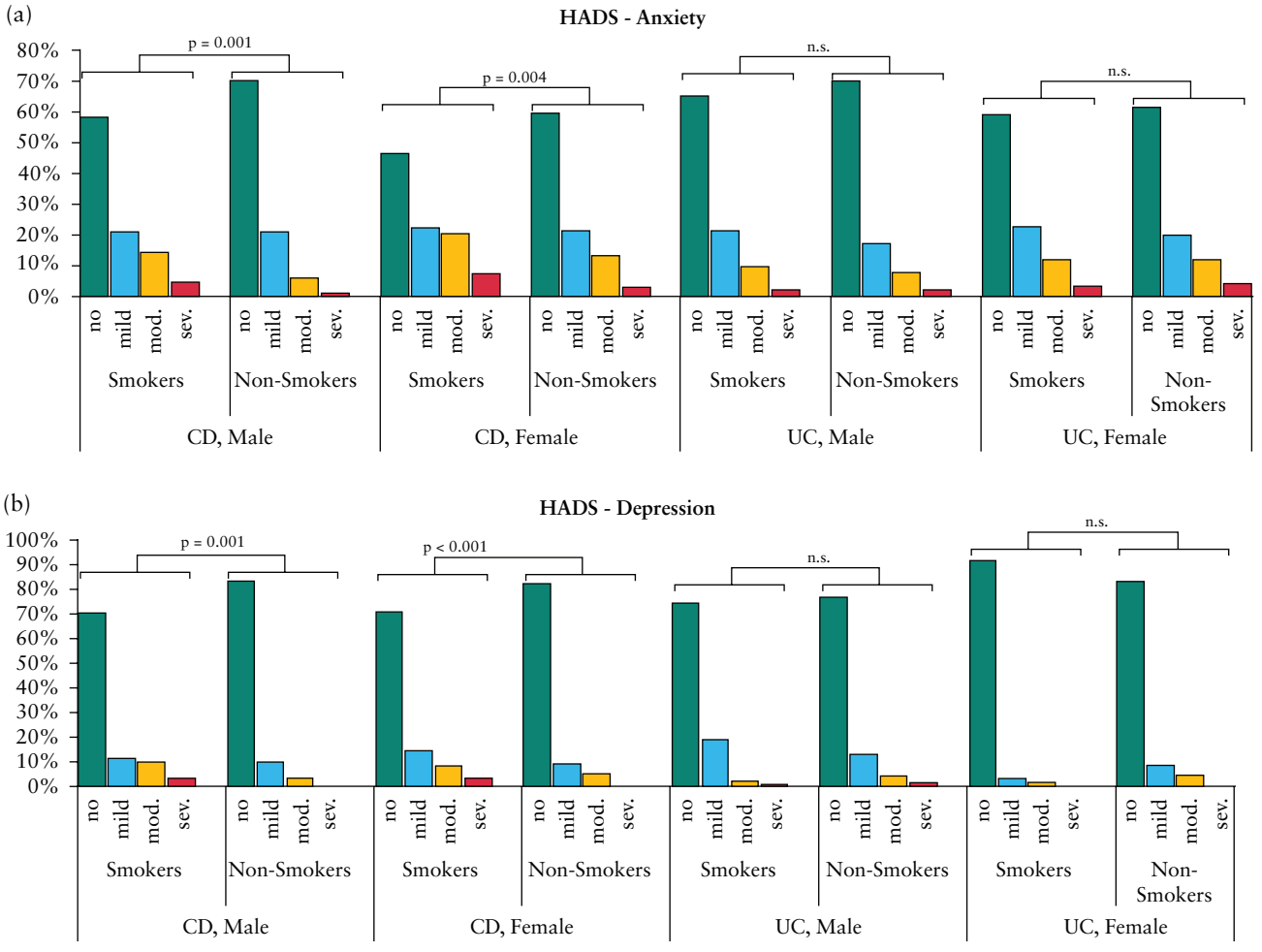

Figure 7. Percentages of no, mild, moderate [mod.] and severe [sev.] degree of anxiety [A] and depressive symptoms [B] according to sex and subtype of inflammatory bowel disease [IBD] in percent [y-axes]. Significant differences are observed in Crohn's disease [CD] only [*p*-values given], whereas there are no significant [n.s.] differences in ulcerative colitis [UC].

Table 2. SF-36 for mood and disability. Sub-scores with mean values [median values in brackets] are depicted with respective *p*-values between smoking and non-smoking patients.

SF-36			Smoker	Non-Smoker	*p*-value
Mood	CD	Male	35 [36]	37.1 [38]	0.005
		Female	32.7 [36.5]	35.8 [38]	<0.001
	UC	Male	37 [37]	36.6 [38]	n.s.
		Female	36.6 [36.5]	35.5 [36]	n.s.
Disability	CD	Male	26.6 [29]	27.3 [29]	0.023
		Female	25.8 [27]	26.7 [28]	0.023
	UC	Male	28 [29]	27.1 [29]	n.s.
		Female	27.3 [29]	27 [29]	n.s.

UC, ulcerative colitis; CD, Crohn's disease; n.s., non significant.

in the SIBDCS. In addition, there might be some heterogeneity, between those patients with a longer follow-up since enrolment and those patients with a more recent inclusion in the SIBDCS. However, there is no evident reason to assume that this potential bias substantially differs between the subgroups of patients we addressed in our analyses. In the general population, the methodology of data collection may be even more challenging and evidently methods applied here for the GSP, as extensively described elsewhere,[35] differ in some aspects from those used in a longitudinal cohort study, which is why any comparisons have to be interpreted with some caution. Also, longitudinal annual follow-up within a cohort study cannot precisely determine the link between cause and effect of smoking and associated factors. For a subset of patients, smoking might serve as a means of addressing psychiatric or abdominal symptoms. A prospective specific study with more frequent [weekly or even daily] quantitative recording of smoking and the outcome variable of interest would be necessary for a more precise analysis. Furthermore, even though we were able to include 1770 patients, the number of individuals in several subgroups is too small for robust conclusions regarding some analyses. Finally, since our study is purely observational, all our conclusions need to be tested in future interventional studies.

One strength of our study is the prospective data acquisition by the SIBDCS throughout the whole of Switzerland, including IBD patients receiving care by gastroenterologists in private practice, smaller hospitals, and also tertiary referral academic centres. Thus within the SIBDCS a wide spectrum of data is available including clinical symptoms, a detailed previous history, history of disease, treatment record, and socioeconomic and psychosocial factors. Moreover, complementary data are acquired from both physicians

and patients, allowing a broad, profound, and reliable investigation of factors associated with smoking in IBD.

In conclusion, we identify an alarmingly high smoking rate in CD, especially in women, persistently elevated throughout our observation period. Moreover, smoking is significantly inversely associated to concomitant PSC in Swiss IBD patients. In addition, impaired mood, disability, anxiety, and depression are revealed to be associated with smoking. The extremely low rate of patients claiming to have received support from their treating physician[s] appears both worrisome and unacceptable, suggesting a need for improvement [considering the well-established deleterious effects of smoking on the course of disease in conjunction with the proven beneficial impact of smoking cessation in CD—but also in UC, where the extensive all-over net benefit of smoking cessation outweighs potential downsides, such as worsening UC activity[13] or subsequent modest weight gain][61] The necessary efforts appear anything but insurmountable, as already minimal interventions, such as 3 min of physician's counselling, are of proven efficacy in successfully enabling smoking cessation.[46]

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Conflict of Interest

None to declare.

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Author Contributions

LB, SRV, MF, and GR formed the concept of the study. NF, VP, PJ, LB, and GR performed pre-evaluations for data extraction from the SIBDCS. LB, BM, PF, JZ, and CNM carried out first analyses of data. NF and LB performed the final statistical analysis. RvK specifically performed analysis of psychological and quality of life measures. LB drafted the manuscript. BM, NF, RvK, PJ, and GR wrote the manuscript. All authors read the manuscript, gave critical input, and approved the final manuscript.

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